Review Article

ROLE OF ENZYMES IN THE PATHOGENESIS OF DEPRESSION

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ABSTRACT

Depression is one of the most prevalent neuropsychiatric disorders that occurs due to the alterations in the monoaminergic system of the body. Various factors may be responsible for the alterations in the monoaminergic system. MAO-A is an enzyme which metabolizes the monoamines and thus responsible for the reduction in the level of monoamines in the body. Stress induces the increase expression and levels of various proinflammatory cytokines such as IL-6, IL-1β, TNF-α and PGE$_2$ involved in the pathogenesis of depression. These proinflammatory cytokines increase or decrease the activity of various enzymes that further led to the reduction in the serotonin level of the brain. Thus, it has been suggested that the depression which is considered as a disorder that arises due to the imbalance in the neurotransmitters in the brain arises due to the alterations in the activities of the various enzymes. Therefore the aim of present review is to demonstrate the role of the various enzymes in the pathogenesis of depression.

Keywords: Depression, Enzymes, Nitric oxide, Stress.

INTRODUCTION

Depression is a heterogeneous and one of the most prevalent neuropsychiatric disorders that affect 20% of the world's population. [1, 2] According to WHO, depression will result in more years of life lost to disability than any other illness by the year 2030. Today, depression is already the second cause of disability-adjusted life years in the age category 15 to 44 y. [3] Depression is a leading cause of morbidity and mortality in youngsters; the risk begins in early teens and continues to rise in a linear fashion. [4] Nearly one in four women and one in six men experience depression during their lifetime; up to 65% of individuals have recurrent episodes; many people never receive diagnosis or treatment for depression and therefore only about 30%-35% adults achieve remission using current pharmacotherapy. [5, 6] The exact mechanism that contributes to depression is not known but alterations in monoaminergic systems contributes to the pathogenesis of depression and, therefore, the drugs that influence the monoaminergic system influences depression-like behavioral alterations [7]. In spite of the introduction of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and specific serotonin-noradrenaline reuptake inhibitors (SNRIs), depression continues to be a major medical problem. Antidepressants generally have slow onset and severe side effects that is continued to be a problem for the patients. [8] Antidepressants generally work by increasing the levels of serotonin (5-HT), norepinephrine (NE) and/or dopamine (DA). TCAs and MAOIs have now limited application because they frequently possess undesirable side-effects and toxic effects. Newer-generation antidepressants, including SSRIs offered more selectivity, improved safety, and tolerability. But the problems such as intolerability, delayed therapeutic onset, limited efficacy and treatment-resistant depression still persist [9]. Thus, there is a need of newer and safer antidepressants and to develop the newer drugs we have to select some new targets. Depression is considered as an imbalance of neurotransmitters, the production of these neurotransmitters is catalyzed by various enzymes. Thus, it has been suggested that alterations in the levels of expression of the neurotransmitters may arise due to the alterations in the enzymes that catalyzed the production and metabolism of these neurotransmitters. Thus, these enzymes may be good therapeutic targets for the pharmacotherapy of depression. Therefore, in the present manuscript authors considered that the depression occurred due to the imbalancein the expression of the various enzymes that directly or indirectly influences the neurotransmitters involved in the pathogenesis of depression

Pathogenesis of depression

Stress is a stimulus that disturbs the homeostasis of the body and induces depressive disorders through the activation of neuroendocrine system, neurotransmitter changes, and proinflammatory cytokines. [10] Stress increases the release of pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IFN-γ, and TNF-α. [11] Also the patients with depression have higher levels of TNF-α and IL-6. [12] Administration of TNF-α and IL-1β in rodents produces the behavioral deficits known as "sickness behavior" including diminished feeding, motor activity, and social behavior. [13] IL-6 also contributes the depression-like behavior in FST. [13] Administration of IFN-α significantly increases the plasma levels of IL-6, IL-10, TNF-α, plasma corticosterone concentration, and sickness behavior. [13] Elevated levels of CRP and IL-6 independently predict the subsequent development of depression. [14] The high incidence of major depression in inflammatory medical illnesses also suggests a role of inflammation in the etiology and pathogenesis of depression. [15] Thus the blockade of production of these pro-inflammatory cytokine results in the alleviation of depressive symptoms.

Indoleamine 2, 3-dioxygenase and depression

Indoleamine 2, 3-dioxygenase (IDO) is an enzyme which metabolizes tryptophan to yield kynurenine (KYN) and, therefore, decreases the availability of tryptophan in CNS. [16] IDO provides an alternative pathway for tryptophan metabolism and this pathway is ultimately responsible for the decrease in the levels of serotonin in the brain. [17] Cytokines such as IFN-γ induces IDO and causes the reduction in tryptophan availability, leading to a reduction in serotonin synthesis in the brain. Activation of IDO led to the depletion of tryptophan rapidly and precipitates depressive symptoms. [17] KYN so formed by the enzymatic action of IDO, is then metabolized to quinolinic acid (QUIN). [17] QUIN was shown to cause an over-release of glutamate in the striatum and cortex, [16] result in the subsequent activation of NMDA receptors which contribute to neurotoxicity. [17] Therefore the blockade of the inflammatory cytokine led to the amelioration of the depressive symptoms, [18] and it may be due to the inhibition of the IDO pathway.

Nitric oxide synthase and depression

Nitric oxide synthase catalyzed the production of nitric oxide (NO) from l-arginine. Nitric oxide synthase (NOS) exists in three different isoforms: NOS1 (nNOS or neuronal NOS), NOS2 (iNOS or inducible NOS) and NOS3 (eNOS or endothelial NOS). [22] NO is synthesized

from iNOS upon the induction of NF-κB, which in turn is activated by the cytokines such as IL-1 and TNF-α [19, 21] Activation of NF-κB pathway increased the expression of iNOS, which when expressed results in the production of the NO in the larger quantity. [20] NO at physiological concentrations acts as a neurotransmitter, signaling component, [22] and regulates, blood flow, neurotransmission, memory formation and prevents apoptosis in the neurons, [23] but production of NO in larger quantities and in an uncontrolled manner contributes to the development of several neuropathological states. [24] Stress-induced pro-inflammatory cytokines are responsible for the induction of iNOS, [27] and the expression of iNOS is responsible for the excessive production of NO for a longer period of time is responsible for the neurotoxic actions, [22, 28, 29] NO generated by iNOS causes the induction of apoptosis. Inhibition of mitochondrial respiration and regulation of oxidative phosphorylation, in addition to its exerts cytotoxic effects on target cells. [30] The cytotoxic effects of NO are tightly related to the production of peroxynitrite, a potent oxidant formed by the interaction of nitric oxide with superoxide anion. [31] Besides iNOS, nNOS is also involved in the production of NO. Activation of NMDA receptors led to the activation of nNOS which when express produces NO. [25] Stress-mediated release of IL-6 further activates NMDA receptors whose activation is further responsible for the production of NO. [26] NO plays an important role in the pathogenesis of mood disorders, [32, 33] and has been implicated in the pathophysiology of depression. [34, 35] Higher concentration of plasma NOx in patients with the recurrent depressive disorder was associated with the severity of depressive symptom suggesting that an overproduction of NO results in oxidative stress and cell damage. Increased production of NO and peroxynitrite may cause nitration and nitrosylation of proteins that appears related to the pathogenesis of depression. [36, 37] NO modulate 5-HT release from specific brain structures, affect 5-HT re-uptake and appears to interact with selective 5-HT re-uptake inhibitors used in the treatment of depression. Several studies have demonstrated that NOS inhibitors produce antidepressant-like actions in a variety of animal paradigms [34].

Monoamine oxidase and depression

Monoamine oxidase (MAO) is an enzyme responsible for the breakdown of monoamines. [38] Two forms of the enzyme, MAO-A and B, are synthesized by two distinct genes. [38] MAO-A is found primarily in the intestinal tract, liver, and peripheral adrenergic neurons whereas MAO-B is found mostly in the brain and liver. [39] Both MAO-A and MAO-B are found in CNS, in particular in neurons and astroglia. [40] MAO-A and MAO-B are FAD-dependent enzymes responsible for the metabolism of neurotransmitters such as dopamine, serotonin, adrenaline, and noradrenaline and for the inactivation of exogenous aryl alkyl amines. Both enzymes are bound to the mitochondrial outer membrane and catalyze the oxidative deamination of their substrates. [41] MAO-A mainly metabolizes 5-HT, dopamine (DA) and norepinephrine (NE), thus the drug which inhibits the action of MAO-A acts as antidepressant. [42] MAO inhibitors emerged in a consistent way as being substantially more effective than conventional reuptake-blocking antidepressants in bipolar depression. [43] Currently, MAO inhibitors are typically reserved for third-or-fourth-line treatment. Drug interactions, side effects, preference for other treatments, and dietary restrictions were the reasons most, often cited for not prescribing these drugs. [39] Selegiline is an irreversible MAO-B inhibitor; the transdermal formulation of it conveys safety. [43] Selegiline enhances dopaminergic neural transmission and thus exerts overall antidepressant effect [44].

COX and depression

Cyclooxygenase (COX) catalyzed the production of prostaglandins by metabolizing arachidonic acid (AA). [45] COX exists in two isoforms, COX-1 and COX-2. [46] COX-1 is constitutively expressed in the gastrointestinal tract whereas the COX-2 predominates at sites of inflammation. [47] COX-1 is a constitutive enzyme, whereas COX-2 is inducible and short-lived. [48] COX-1 is responsible for the biosynthesis of PGs in gastric mucosa and kidney, whereas COX-2 is responsible for the biosynthesis of PGs in inflammatory cells and CNS. [49] COX-2 has been shown to interact with neurotransmitters such as acetylcholine, serotonin, and glutamate. [50] COX-2 plays an important role in the pathogenesis of the depressive disorder. [51] Also the chronic celecoxib treatment reverse the effect of the chronic unpredictable stress-induced depressive-like behavior therefore, the selective COX-2 inhibitors could be developed as potential remedies for the treatment of depression. [52] Chronic treatment with celecoxib reduced depressive-like behavior and caused a dose-dependent decrease in the expression of COX-2 and concentration of PGE2 in stressed rats. [53] Both PGE2 and COX-2 participate in the signaling of inflammatory processes, and they are likely implicated in neuronal death and inflammation-mediated cytotoxicity. [54] IL-6 increase the activity of COX-2 and it, in turn, activates the release of IL-1β and TNF-α as well as PGE2. [17] Besides inhibiting the enzyme COX-2, COX-2 inhibitors influence serotonergic system by inhibit the release of IL-1 and IL-6 and the CNS from effects of QUIN, thus exerts the beneficial effect in the depression. [50].

Tryptophan hydroxylase and depression

Tryptophan hydroxylase (TPH) is a very strong and emerging target for the treatment and study of mood disorders. [55] TPH catalyzes the rate-limiting step in 5-HT synthesis, and thus its alterations play a major role in the pathogenesis of several psychiatric disorders. [56, 57, 58] TPH1 and TPH2 are expressed in the human brain, and genetic variation in both isoforms has been associated with alterations in mood and 5-HT function. Classical TPH gene, called TPH1, is expressed in the gut, pineal gland, spleen, and thymus while the second TPH gene called TPH2 is predominantly expressed in the brain stem. [57, 59] The gene for TPH2 contains a number of polymorphisms that might serve as useful markers for complex behavioral phenotypes. [62] The human TPH2 gene spans 97 kilobases (kb), consists of 11 exons, and is located on chromosome arm 12q15. [61] A single nucleotide polymorphism in human TPH2 alters, TPH enzymatic efficiency and is found to be associated with the depression. [60] Genetic variation that influences TPH enzymatic activity results in the development of the mood disorders. [63] The genetic deletion of TPH2 strongly reduces the amount of 5-HT and 5-HIAA in the brain, but does not reduce their levels in the periphery; however the combined deletion of TPH1 and TPH2 resulted in a near total loss of 5-HT and its metabolite, in both brain and periphery. [64] It has also been reported that TPH2 KO animals show no loss of serotonergic cells in the raphe nucleus of the brain in spite of total loss of 5-HT. TPH2KO mice did not differ significantly in peripheral 5-HT levels. However levels of 5-HT and its metabolite, 5-HIAA, were strongly reduced in all brain regions examined. [65] In a recent report, a TPH2 knockin mouse line with reduced TPH2 activity and an 80% reduction in brain 5-HT, due to a rare human SNP (R441H), was reported to have significantly increased immobility times in the TST. [65] Genetic inactivation of TPH2 function in mice led to enhanced conditioned fear response, increased aggression and depression-like behavior. [66] TPH2 R439H mice (Tph2 knockin mice henceforth) have markedly reduced 5-HT synthesis and tissue levels and exhibit increased depression-like behaviors. [67] Detection of linkage of TPH2 haplotypes to major depression provided evidence of a functional locus somewhere within TPH2 [68]. It has been found that the human TPH2 gene coding region contains a functional polymorphism, G1463A, leading to the replacement of the 441 arginine position with histidine (R441H). TPH2 function loss and significantly reduce 5-HT generation. [69, 70] The functional SNP in mouse TPH2 mediated reduction of 5-HT levels provides direct evidence that TPH2 controls brain serotonin synthesis, [71] and, therefore, the decreased TPH2 activity reduces the 5-HT in the brain. [72]. Therefore, the enzyme TPH can be served as a new target for the treatment of depression.

AKT/GSK3 and depression

The serine/threonine kinase (Akt) also known as protein kinase B plays an important role in many cellular processes such as proliferation and survival. [73] Akt is most widely associated with the phosphatidylinositol 3-kinase (PI3K) signaling pathway, and it is activated by the enzyme PI3K that catalyzes the production of phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate. Glycogen synthase kinase-3β (GSK-3β) is the

substrate of Akt, [74] and affects many cellular functions such as cell cycle, gene transcription, and cytoskeletal integrity. [75] Activity of GSK-3β is increased by the phosphorylation of Tyr216 while GSK-3β is inhibited by the phosphorylation of Ser9. PI3K/Akt signaling is responsible for the phosphorylation of Ser9 and, therefore, is responsible for the inhibition of GSK-3β. [75] Several different kinases including Akt (protein kinase B), protein kinase C, and protein kinase A are capable of phosphorylating serines on GSK-3β. [76] 5-HT1 and 5-HT2 receptors are involved in regulating the activity of GSK-3β. [77] Activation of 5-HT1 receptors inhibits GSK-3β activity whereas the activation of 5-HT2 receptors activates GSK-3β. [73] Stimulation of 5-HT1 receptors enhances phosphorylation of Ser-9 residue and causes the inhibition of GSK3β and the stimulation of 5-HT2 receptor reduces phosphorylation of Ser-9 residue, results in the inactivation of GSK3β. Therefore, the deficiency of 5-HT exerts differential effects on GSK-3β activity. [78] Akt/GSK3β pathway has been found to be altered in the patients of psychiatric illnesses. Antidepressants generally upregulate the expression of phosphorylated Akt protein. [79] Cyclic AMP response element binding protein (CREB) is a key transcription factor involved in several critical functions of the brain and it is known to be activated by PI3K/Akt signaling pathway. [80] Antidepressants inhibits the GSK3β and contribute to the increases in CREB. Thus, in mood disorders impaired inhibitory control of GSK3β may reduce CREB activity [77]. Therefore the drugs that inhibits the expression of GSK-3β exerts beneficial effects in depression.

MMPs and depression

MMPs are a family of neutral proteases that contributes to interactions between cells and their matrix, allowing movement and shape changes in processes such as development and neuronal plasticity. Oxygen radicals, NO and proteases have been implicated in MMP activation. [81] MMP-9 serum levels significantly correlated with the depressive phases in younger subjects (<45 y), [82] Specifically, depressed patients reporting higher levels of chronic stress, current stress, and negative affect showed higher MMP-9 expression. Stress induces NE release, which acts on α1-and β-adrenergic receptors on human monocytes and, therefore, activates NF-κB, which mediates the expression of MMP-9 as well as IL-6. [87] NF-κB, is itself the primary transcriptional regulators of MMP-9 expression. [83] Depressed patients are unable to express appropriately NF-κB at mRNA levels which may, in turn, lead to defective molecular expression. [84] Activation of NF-κB results in the induction of many inflammatory cytokines which activate a central inflammatory response associated with altered metabolism of serotonin involved in depression. Stress-induced NF-κB activation leads to depressive-like behavior in rodents and inhibits neurogenesis in brain regions involved in depression. [85] Stress-induced anhedonia, a core symptom of depression, is also dependent on NF-κB [86]. Therefore, the selective inhibition of NF-κB and MMPs may exert beneficial effects in the pharmacotherapy of depression.

Glutamine synthetase and depression

Glutamate is the major excitatory neurotransmitters in the brain and plays an important role in the regulation of several important CNS processes linked to the pathogenesis and pathophysiology of several disorders. [88] Recent clinical and post-mortem studies of depressed patients have found that the depressed patients have increased serum and plasma levels of glutamate compared with controls. [89] Glutamate is formed inside the neurons, from the glucose through the process of transamination and by the conversion of glutamine to glutamate by the enzyme glutaminase. [90] Glutamate is released from the neurons upon depolarization in a calcium-dependent manner into the synapse and removed from the extracellular space by highly efficient excitatory amino acid transporters (EAAT1–2). After uptake by EAATs, glutamate is rapidly converted into the 'inert' intermediate glutamine by enzyme glutamine synthetase in the glial cells. Glutamine is converted back into glutamate and the glutamate so formed is transferred into the synaptic vesicles through vesicular glutamate transporters (VGLUT1–3). [90] Glutamine synthetase thus provides neuroprotection by influencing the clearance of extracellular

glutamate into glutamine in cortical astrocytes. Therefore, a decline in the expression of glutamine synthetase at the site of injury may significantly reduce the ability of glial cells to remove extracellular glutamate, thereby exacerbating the process of neuronal degeneration. [92] Higher level of extracellular glutamate could be a cause of depressive behaviors and it may be due to the lower levels and/or lower activity of glutamine synthetase. Thus, the enzyme glutamine synthetase plays an important role in mood regulation and should be further investigated for the prevention and treatment of depressive disorders [91].

Histone acetyltransferases and histone deacetylases and depression

DNA is tightly associated with histones embedded deep within chromatin. [93] Chromatin modifications are important for elevating mood in clinical depression. [94] Alterations in the level and activity of histone deacetylase affect depression-related behaviors. [95] Histone acetylation is a dynamic process, controlled by specific enzymes histone acetyltransferases (HATs) and histone deacetylases (HDACs) which either add or remove the acetyl group. [93] Acute psychological stressors cause the acetylation of lysine 14 of histone H3 (H3K14) and an overall increase in acetylation in nucleus accumbens has been associated with depressive-like symptoms in mice. [96] Thus histone acetylation has become a promising target for the novel treatments of psychiatric disorders. [97] Exposure of mice to chronic social defeat stress alters acetylation of histones in nucleus accumbens, [98] and show reduced mobility in a forced swim test; this may be due to chromatin modification. [99] Therefore chronic social stress produces a transient reduction in NAc that H3 acetylation after social defeat stress in NAc that may contribute to depressive symptoms. [97] Administration of HDAC inhibitors (HDACi) into NAc thus exerts an antidepressant effect, also the systemic or intracerebral administration of various HDACi, either alone or in combination with antidepressants, improved antidepressant responses in a variety of animal models. [100] Chronic social defeat stress led to a transient increase in the level of histone acetylation followed by a persistent decrease the histone acetylation in the hippocampus.

These changes were reversed by imipramine. Thus the same subsets of genes in different brain regions mediate opposite effects on depression-related behavior. [100] HDAC5 expression is decreased in the hippocampus of chronically defeated mice that receive chronic imipramine treatment, and HDAC5 over expression in the DG blocked the behavioral efficacy of imipramine treatment. [101] Treatment with HDAC inhibitors is associated with neuroprotective effects and may be beneficial in the treatment of various psychiatric disorders. Therefore, it has been suggested that the HDAC5 is likely to be involved in a behavioral pathway common to multiple psychiatric disorders [102]. Antidepressants increase H3 acetylation at BDNF promoters, and this effect was associated with a decrease in expression of HDAC5. This downregulation in HDAC5 was shown to be necessary for the behavioral effects of chronic antidepressant treatment [103].

CONCLUSION

Depression occurs due to alterations in monoaminergic systems. The production of monoamines is catalyzed by various enzymes and therefore, increase or decrease in activity of these enzymes is responsible for alterations in the levels of monoamines. Stress is an important factor that disturbs the homeostasis of the body. Stress has been shown to increase the production of pro-inflammatory cytokines, which are responsible for the activations of enzymes responsible for the degradation, inactivation, inhibition of action or release of monoamines in body, or these pro-inflammatory cytokines inhibit the enzymes responsible for the production or synthesis of monoamines in body. The present manuscript explains how different enzymes influence the depression-related behaviors. Therefore, this manuscript supports that the increase or decrease in the activities of certain enzymes results in the depressive behaviors. and these enzymes can be served as a good target for the drug development for the pharmacotherapy of the patients of depression.

CONFLICT OF INTERESTS

Declared none

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